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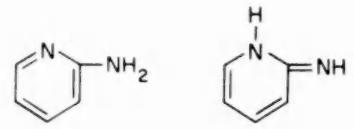
ADDITION OF 2-AMINOPYRIDINE TO UNSATURATED ESTERS

By GERALD R. LAPPIN*

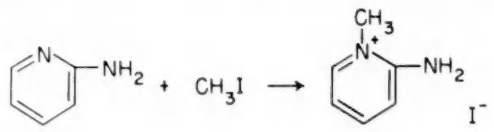
The addition of primary amines to unsaturated esters to give β-amino esters is well known. However, the use of 2-aminopyridine in such reactions has been but little studied. Although 2-aminopyridine is normally written, and probably exists as, the amino form, its chemistry is complicated because of its potential tautomerism. In its reactions, 2-aminopyridine can give products derived from either the amino form or the imino form.



Amino form Imino form

Before discussing the reactions of 2-aminopyridine with unsaturated esters, a brief examination of the complications introduced by this tautomerism may be of interest.

In most reactions, the point of attack of an electrophilic reagent is at the amino nitrogen, to give a product which retains the resonance-stabilized pyridine ring. Attack at the ring nitrogen has been reported to occur only in those reactions in which the product is a quaternary salt, retaining the pyridine resonance, or in reactions involving both the ring and the amino nitrogens, which result in cyclic products having the imino form. For example, methyl iodide reacts with 2-aminopyridine at the ring nitrogen to give a salt which still retains the aromatic ring (1).



Phenacyl bromide reacts to give an imino-form (2) product, but it is not known which nitrogen is the initial point of attack.

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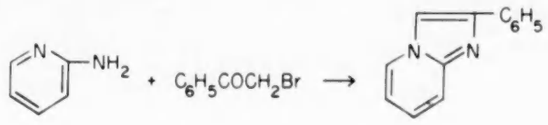
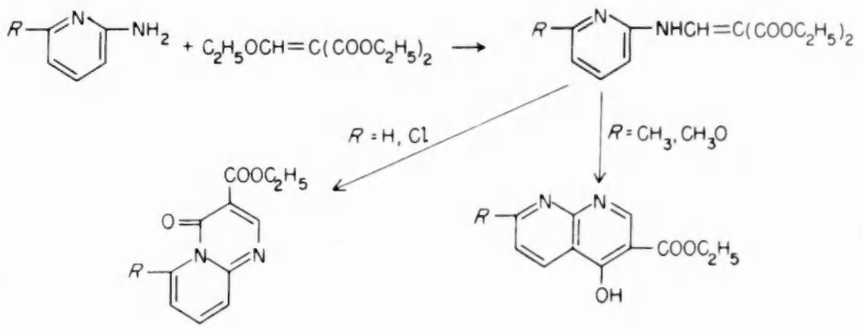


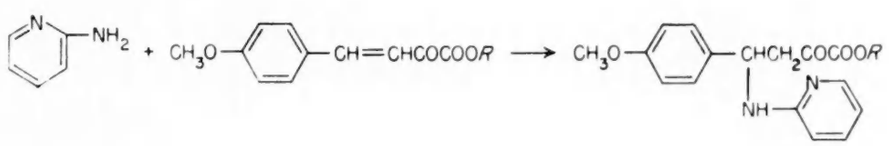
In some reactions of 2-aminopyridine which result ultimately in the formation of a second ring, a noncyclic intermediate can be isolated. This intermediate is the product of attack at the amino nitrogen.

Subsequent ring closure usually involves attack at the ring nitrogen to give a pyridopyrimidine. However, if electron-releasing substituents are present in the 6-position, so that the electron density at the third carbon atom is greatly increased, attack occurs at this carbon atom to give a 1,8-naphthyridine. An example of such a reaction is the stepwise reaction of a 2-aminopyridine with diethyl (ethoxymethylene)malonate (3). In previously reported reactions, either an imino-type or

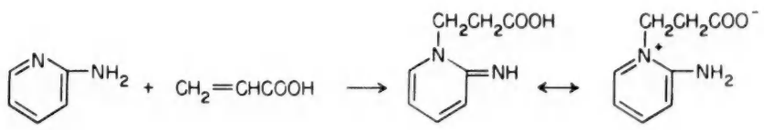


amino-type product has been found, but no single reaction has given both types of products simultaneously.

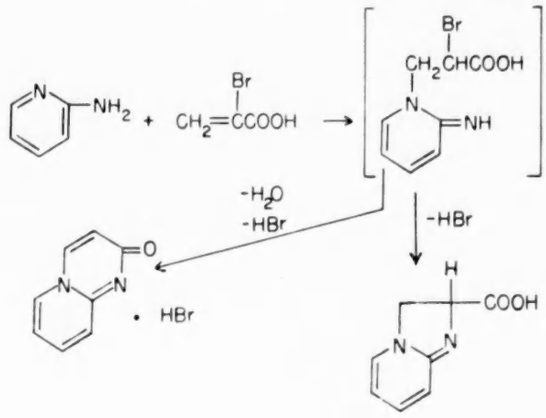
Only a few additions of 2-aminopyridines to unsaturated esters or related compounds have been reported. An amino-type product was obtained by C. F. H. Allen and co-workers (4) from the reaction of 2-aminopyridine with anisylidenepyruvic ester.



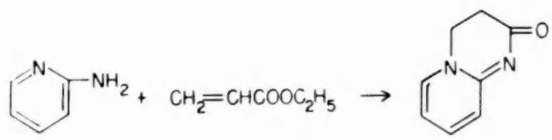
In contrast, Adams and Pachter (5) showed that the addition of 2-aminopyridine to acrylic acid occurs through attachment at the ring nitrogen. Although they wrote the product as an imino-form acid, it probably has the aromatic zwitterion structure.



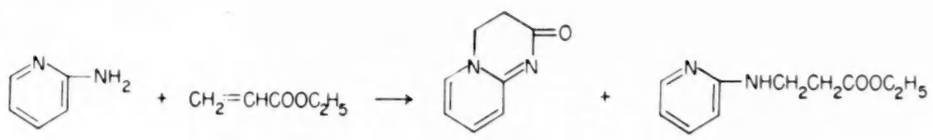
The reaction of 2-aminopyridine with 2-bromoacrylic acid was shown to give two bicyclic products, both having the imino structure and both presumably derived from an intermediate similar to the acrylic acid adduct (5).



The addition of 2-aminopyridine to ethyl acrylate reportedly gave only a dihydropyridopyrimidine derivative (5). A more detailed study (6) of this last reaction showed that it followed a more complex course than originally proposed. When



2-aminopyridine was heated with ethyl acrylate, as described by Adams and Pachter, insoluble 3,4-dihydro-2H-pyrido[1,2-*a*]pyrimidin-2-one (I) was obtained, but in lower yield than reported. Distillation of the liquid portion of the reaction product gave an almost equal amount of a second, lower-melting product which gave the correct analysis for the noncyclic adduct of 2-aminopyridine and ethyl acrylate. Hydrolysis of this adduct gave an acid isomeric with the acid obtained from 2-aminopyridine and acrylic acid, 2-imino-1(2H)-pyridinepropionic acid. This new acid could be only N-(2-pyridyl)-β-alanine and the low-melting adduct was its ethyl ester (II). This is the first reported reaction of 2-aminopyridine which gives



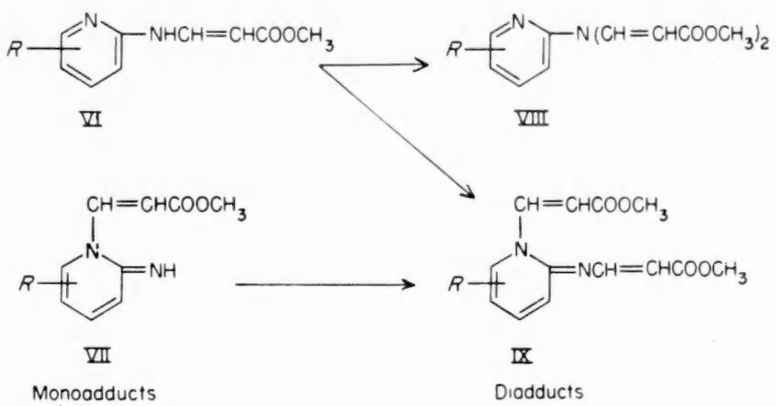
I II

both imino- and amino-form products simultaneously. It was found that the ratio of I to II depended on the heating time if the ethyl alcohol evolved was not allowed to distill off. Heating for a short time gave largely the pyridopyrimidine (I), but heating for 100 hr. gave only the ethyl ester of N-(2-pyridyl)-β-alanine; however, the formation of II was not reversible. Prolonged heating of II gave no cyclic product.

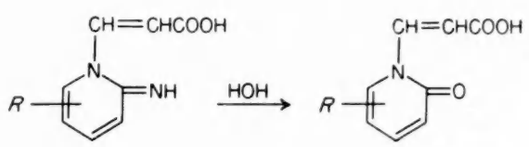
When the various methyl-2-aminopyridines were heated with methyl acrylate, similar results were obtained in most cases; however, 6-methyl-2-aminopyridine gave only the noncyclic adduct, while 3-methyl-2-aminopyridine gave only the dihydropyridopyrimidine. These anomalies may reflect the result of steric hindrance

acid (IV). The colored product had the correct analysis for an adduct of two moles of methyl propiolate per mole of 2-aminopyridine. When this reaction was applied to the various methyl 2-aminopyridines, a methyl 2H-pyrido[1,2-*a*]pyrimidin-2-one was obtained in every case. With 6-methyl-2-aminopyridine, this was, unexpectedly, the only product. With the other methyl-2-aminopyridines, a colored, noncyclic product was also obtained. However, analysis showed that only 5-methyl-2-aminopyridine gave a 2:1 adduct (diadduct) like that given by 2-aminopyridine; the others were 1:1 adducts (monoadduct). This difference in behavior is, at present, not understood.

It was found that the monoadducts could be converted to diadducts by reaction with more methyl propiolate. The following structures were considered for these adducts:



The amino-form adducts, VI and VIII, seemed to be ruled out by the deep orange-to-red color of the products obtained. The infrared and ultraviolet spectra also favored the imino structures, VII and IX. The structures of the monoadducts were established by their ready hydrolysis to a derivative of 2(1H)-pyridone. With the



structure of the monoadducts shown to be VII, the diadducts could have only structure IX. This is the only known reaction of 2-aminopyridine which gives an imino-type, open-chain derivative for which no structure which preserves the pyridine ring resonance can be written. No explanation can now be offered for the formation of these thermodynamically less stable adducts in preference to the more stable amino-form adducts which are normally obtained.

The addition of 2-aminopyridine to methyl propiolate must not be stereospecific but, rather, must give both *cis* and *trans* adducts. The geometry of the *cis* adduct is favorable to cyclization and this isomer is immediately transformed into the cyclic product. However, the *trans* isomer is not favorably arranged for ring closure and it is isolated as the noncyclic monoadduct or converted to the diadduct. This

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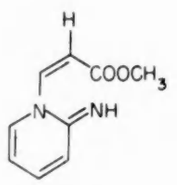
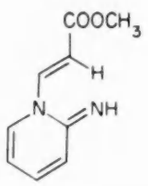
conclusion seems to be verified by the failure of the isolated noncyclic adducts to give cyclic products under any conditions so far tried.



cis adduct



trans adduct

The reaction of 2-aminopyridines with unsaturated esters provided two unexpected results. In the reaction with ethyl acrylate, both an amino-form derivative and an imino-form derivative were formed simultaneously. The addition of 2-aminopyridines to methyl propiolate results in the formation of the first reported noncyclic derivatives of the imino form. Another unexpected result of this reaction was the formation of a pyridopyrimidinone from 6-methyl-2-aminopyridine, which, in similar reactions, has not previously given this type of product.

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